Absence of effect of somatostatin analogue (SMS 201-995) in diarrhea associated with inflammatory bowel disease

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ABSTRACT: The octapeptide long acting somatostatin analogue, SMS 201-995 promotes intestinal fluid and electrolyte absorption and inhibits anion secretion. It is more potent than native somatostatin and does not exhibit tachyphylaxsis. SMS 201-995 was used to treat two patients with severe diarrhea associated with Crohn's disease after other treatments had failed. The volume and frequency of ileostomy output in one patient and stool output in the other did not respond to therapy with SMS 201-995. In fact, diarrhea appeared to increase in both patients while on treatment. Can J Gastroenterol 1989;3(2):53-57

Key Words: *SMS 201-995, Absorption, Diarrhea, Inflammatory bowel disease, Intestine, Somatostatin analogue*

Absence d'effet de l'analogue de la somatostatine (SMS 201-995) dans la diarrhée associée à la maladie inflammatoire de l'intestin

RESUME: L'analogue octapeptide à effet prolongé de la somatostatine, le SMS 201-995 (Sandostatin) favorise les fluides de l'intestin et l'absorption électrolytique et inhibe la sécretion d'anions. Il est plus puissant que la somatostatine naturelle et ne produit pas de tachyphylaxie. Le SMS 201-995 a été utilisé dans le traitement de deux patients souffrant de diarrhée sévère associée à la maladie de Crohn après que tous les autres médicaments ont échoué. Le volume et la fréquence de l'écoulement de l'iléostomie chez l'un deux et des selles chez l'autre n'a pas réagi à la therapie au SMS 201-995. En fait, la diarrhée semble avoir empiré dans les deux cas au cours du traitement.

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Received for publication October 19, 1988. Accepted February 22, 1989

IN VITRO, LONG ACTING SOMATOSTATIN analogue SMS 201-995 (Sandostatin; Sandoz Inc) has an antisecretory effect on intestinal electrolyte transport similar to native somatostatin. That is, it inhibits electrogenic anion secretion and stimulates neutral sodium and chloride absorption (1). Furthermore, this antidiarrheal effect of SMS 201-995 is approximately 60 times more potent than native somatostatin and it does not exhibit tachyphylaxis (1). Clinically, SMS 201-995 has been used to control life threatening diarrhea due to colonic pseudo-obstruction (2), cryptosporidia infection in a patient with AIDS (3,4), idiopathic secretory diarrhea in an infant (5), idiopathic diabetic diarrhea (6), vasoactive intestinal peptide secreting tumours (7-11) and short bowel syndrome (12,13).

This report describes two patients treated with SMS 201-995 for diarrhea due to Crohn's disease. In both patients fecal output and stool frequency failed to improve and tended to increase during SMS 201-995 therapy.

CASE PRESENTATIONS

Case number 1: The patient was a 62-year-old caucasian female who had

suffered profuse ileostomy output since May 1985.

In 1944, the patient developed a perirectal abscess and underwent three surgical drainage procedures. Subsequently, severe incontinence developed as a result of anal sphincter disruption. The incontinence was treated in 1960 with a total colectomy and Brooke ileostomy.

After surgery, the patient was free from symptoms until late 1980 when she noticed the onset of abdominal cramps and increased liquidity of the ileostomy effluent. In March 1985, high output ileostomy losses resulted in hospitalization for severe volume depletion. Following rehydration with intravenous fluids she was discharged, however, her symptoms soon recurred.

In May 1985, the patient was again hospitalized with voume depletion secondary to high ileostomy output. Ileoscopy demonstrated a limited 50 cm segment of acute ileitis with histologic findings compatible with Crohn's disease. In September 1985, 50 cm of ileum was removed with revision of the ileostomy. Nevertheless, diarrhea continued with repeated hospital admissions for volume depletion requiring intravenous rehydration. In September 1987, ileoscopy demonstrated 50 cm of active Crohn's disease with normal small intestinal mucosa above this point.

Ileostomy output of 4000 g/day was reduced to 200 g/day using oral replacement solution (Gastrolyte, Rorer) on a v/v replacement schedule. Further investigations failed to identify an etiology to explain the high ileostomy output (Table 1). Therapeutic trials of lactose free diet, low fat diet, metronidazole, tetracycline, cholestyramine, loperamide, diphenoxylate, codeine, anticholinergic agents, Metamucil (G.D. Searle), 5-aminosalicylic acid, steroids and azothioprine failed to improve ileostomy output.

The patient was then placed on SMS 201-995 in an attempt to control the high volume ileostomy output.

Case number 2: The patient was a 30-year-old caucasian male with Crohn's ileal colitis who had suffered from continuous profuse watery diarrhea up to 12 times daily since 1981. He was initially treated with prednisone and salazopyrin, however, he continued to have eight to 12 bowel movements per day.

In March 1983, colonoscopy demonstrated scattered aphthous ulcers in the transverse colon and an acute distal ileitis extending proximally 10 cm. Stool volume was documented at 2500 g/day. The patient was treated with prednisone, salazopyrin and metronidazole.

In April 1985, the patient continued to have five to 10 bowel movements daily with stool volumes of 500 g/day. Colonoscopy and ileoscopy failed to demonstrate macroscopic or histologic evidence of active Crohn's disease. Further investigations failed to identify a specific etiology for the diarrhea (Table 1). A therapeutic trial of cholestyramine resulted in a temporary, four month improvement in symptoms. Nevertheless, the diarrhea returned and therapeutic trials of lactose free diet, low fat diet,

TABLE 1
Diarrhea Investigation profile

Test	Case 1	Case 2
Stool volume		
Regular diet	1850 mL/day	545 mL/day
Fasting	750 mL/day	540 mL/day
Fat (0-20mmol/L)	199 mmol/day	62 mmol/day
Osmolality	474 mmol/kg	—
Na/K/Cl	101/34/73 mmol/L	—
Guaiac	Negative	Negative
Reducing sub	Negative	Negative
pH	6.4	—
NaOH reaction	Negative	Negative
Bile acids (0.2-1.0)	—	4.68 mmol/day
Culture	Negative	Negative
Ova and parasites	Negative	Negative
Clostridium difficile toxin	Negative	Negative
Blood		
$Na/K/Cl/HCO_3$	Normal	Normal
Immunoglobulins	Normal	Normal
T_4, T_3RU	Normal	Normal
AST	Normal	Normal
Folate	Normal	Normal
Vitamin B12	Normal	Normal
Gastrin	Normal	Normal
Cortisol	Normal	Normal
Magnesium	Normal	Normal
Eosinophil count	Normal	Normal
Special assays		
VIP	Negative	Negative
Urine		
5-HIAA	Negative	Negative
X-rays		
SBFT	Crohn's disease	Normal
Abdominal sonogram	Normal	Normal
Small bowel studies		
Jejunal biopsy	Normal	Normal
Lactose breath H_2	Normal	Normal
Upper endoscopy	Normal	Normal
Therapeutic trials		
Lactose-free diet	No benefit	No benefit
Low fat diet	No benefit	No benefit
Metronidazole	No benefit	No benefit
Antibiotics	No benefit	No benefit
Cholestyramine	No benefit	No benefit
Antidiarrheals	No benefit	No benefit
Anticholinergic	No benefit	No benefit
Metamucil/bulk agents	No benefit	No benefit
Corticosteroids	No benefit	No benefit

T_4 Thyroxine; T_3RU Triiodothyronine resin uptake; VIP Vasoactive intestinal peptide; 5-HIAA 5-Hydroxy indolacetic acid; SBFT Small bowel follow through; AST Aspartate aminotransferase

metronidazole, tetracycline, diphenoxylate, loperamide, codeine, anticholinergic agents. Metamucil and steroids failed to improve symptoms.

It was decided to start the patient on SMS 201-995 in an attempt to control his severe diarrhea.

MATERIALS AND METHODS

SMS 201-995 is a synthetic octapeptide with the structure D-phenylalanyl-L-hemicystyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-thereonyl-L-hemicystyl-L-threoninyl acetate.

After the patient gave informed consent, the drug (100 μg SMS 201-995 dissolved in 1 mL acetate buffered sodium chloride pH 4.0) was administered subcutaneously at 09:00 and 21:00 each day. The initial dose was 25 μg bid and was increased in steps of 25 μg bid at two day intervals until a maximal dose of 250 μg bid was reached. This dose was maintained for 30 days, after which SMS 201-995 was slowly withdrawn over 72 h. A 14 day drug-free interval followed and SMS 201-995 was restarted for an additional 30 day period.

Stool output was collected in preweighed containers (Sage Products, Cary, Illinois) and weights of the containers recorded by the patient with a scale supplied by the investigators. Stool weight, frequency, consistency and food intake were recorded daily in a diary. The diary began 14 days prior to drug administration and continued for the study duration. To ensure compliance, one of the investigators communicated by telephone with the patient three times weekly. The patients and their diaries were reviewed every two weeks in the gastroenterology research clinic, University of Alberta, Edmonton, Alberta.

During treatment with SMS 201-995, measurements of serum electrolytes, blood urea nitrogen, carotene, glucose, calcium, phosphate, total protein, albumin, cholesterol, uric acid and complete blood count were obtained at baseline, once during the first week of the study and then monthly.

RESULTS

The effect of SMS 201-995 on mean stool weight and frequency is shown in Figures 1 and 2 for cases 1 and 2, respectively. In both patients, there was no significant change in stool weight or stool frequency. Nevertheless, there was a trend towards worsening of stool output in both patients while on SMS 201-995.

Both patients complained of mild irritability which resolved spontaneously when the drug was removed. There was no alteration in the measured biochemical parameters and while weight remained stable in the first patient, a loss of 5 kg was documented in the second patient.

DISCUSSION

This study demonstrated that SMS 201-995 given by subcutaneous injection did not alter stool weight or frequency in a patient with Crohn's ileal colitis nor in another with Crohn's ileitis and an ileostomy. Indeed, there was a trend towards worsening of stool output with an associated 5 kg weight loss in one patient.

SMS 201-995 is significantly more potent in vitro as an intestinal antisecretory agent than native somatostatin (1). This finding, along with the ability to administer SMS 201-995 subcutaneously, has led it to the forefront of potential antidiarrheal agents. Despite early enthusiasm, this study suggests that SMS 201-995 may not be effective in severe diarrhea associated with inflammatory bowel disease (IBD).

Recently, intravenous infusion of SMS 201-995 reduced ileostomy output in five patients with severe ileostomy diarrhea, however, when administered subcutaneously ileostomy output in three of these five patients was not significantly improved (12). This may be explained by a lower effective concentration of SMS 201-995 at the level of intestinal enterocytes during subcutaneous injection. Nevertheless, increasing the frequency and total dose of SMS 201-995 failed to reduce ileostomy output (12).

The malabsorption of fat which is known to occur with somatostatin (12,14) may further aggravate the diarrhea in patients with IBD and precipitate weight loss. Although fat excretion was not measured while on SMS 201-995, fat malabsorption may be one mechanism to

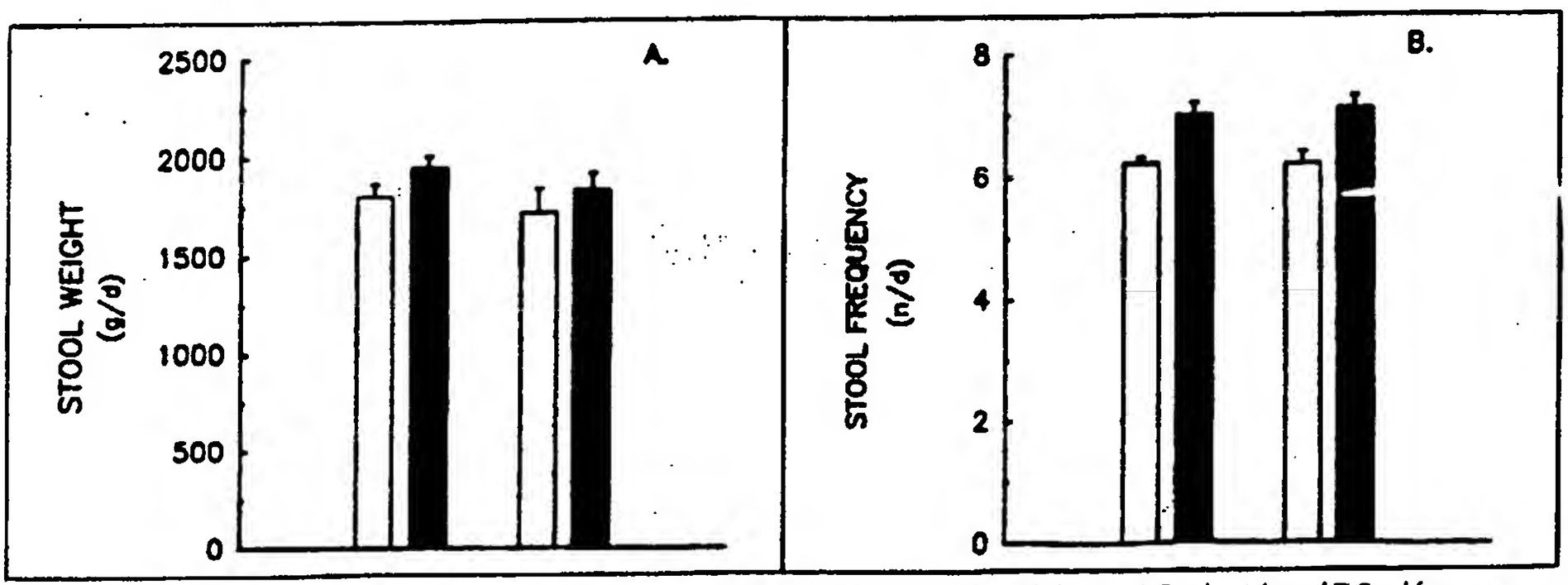

Figure 1) *Effect of SMS 201-995 on ileostomy output in a patient (case 1) with small intestinal Crohn's disease. A Stool weight and B Stool frequency were measured continuously during two consecutive cycles of a 14 day drug-free interval (open bars) followed by a 30 day SMS 201-995 (250 μg bid) treatment interval (solid bars). Values represent mean ± SEM*

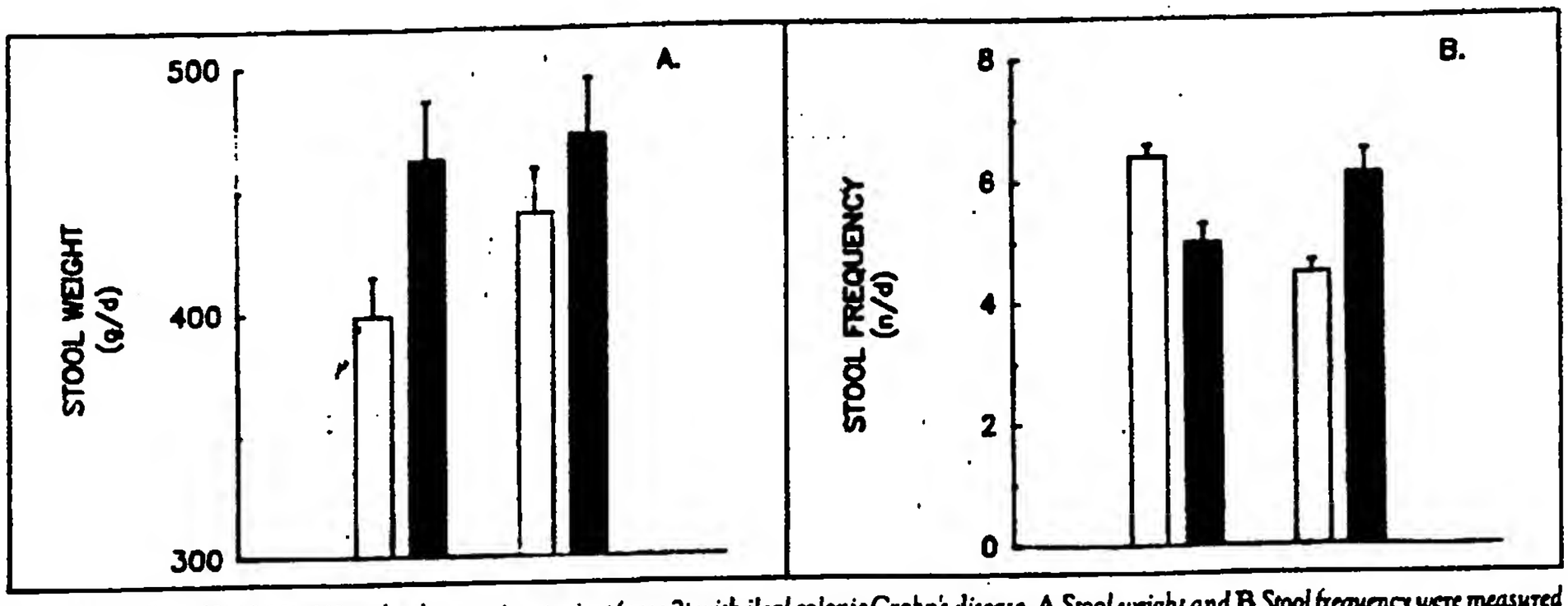

Figure 2) *Effect of SMS 201-995 on fecal output in a patient (case 2) with ileal colonic Crohn's disease. A Stool weight and B Stool frequency were measured continuously during two consecutive cycles of a 14 day drug-free interval (open bars) followed by a 30 day SMS 201-995 (250 μg bid) treatment interval (solid bars). Values represent mean ± SEM*

explain the trend towards increased stool output.

Recently, Clements and Elias (15) reported an adult patient with pancreatic cholera and metastatic VIPoma who had a delayed clinical and biochemical response to SMS 201-995 after one month of treatment. Although the patients in the present study continued SMS 201-995 for a 30 day period, one of the patients (case 1) continued the SMS 201-995 off study for 60 consecutive days without reduction in stool output.

The major therapeutic benefit of SMS 201-995 remains in treating patients with acromegaly and gastrointestinal endocrine tumours (6-10,16-24). Its efficacy as an antidiarrheal agent for nonhormonally mediated secretory diarrheas is at best intermittent. The recent development of an aqueous solution of SMS 201-995 with rapid absorption of the gastrointestinal tract after local application may prove beneficial in delivering greater concentrations to the enterocyte and hence improve the clinical antidiarrheal action of SMS 201-995 (25).

ACKNOWLEDGEMENTS: Dr Fedorak is a recipient of the Alberta Heritage Foundation for Medical Research clinical investigatorship. This work was supported by a grant from the Alberta Heritage Foundation for Medical Research. SMS 201-995 was generously supplied by Sandoz Pharmaceuticals Canada Inc, Dorval, Quebec.

REFERENCES

1. Roberts WG, Fedorak RN, Chang EB. In vitro effects of the long-acting somatostatin analogue SMS 201-995 on electrolyte transport by the rabbit ileum. Gastroenterology 1988;94:1343-50.
2. Mulvihill S, Passaro E, Debas H, Yamada T. Severe diarrhea after colonic pseudoobstruction: Treatment with somatostatin. N Engl J Med 1984;310:467-8.
3. Rene E, Bonfils S. Control of severe diarrhea with somatostatin. N Engl J Med 1984;311:598.
4. Cook DJ, Kelton JG, Sunisz AM, Collins SM. Somatostatin treatment for cryptosporidial diarrhea in a patient with acquired immunodeficiency syndrome. Ann Intern Med 1988;108:708-9.
5. Jaros W, Biller J, Greer S, O'Dorisio T, Grand R. Sucessful treatment of idiopathic secretory diarrhea of infancy with the somatostatin analogue SMS 201-995. Gastroenterology 1988;94:189-93.
6. Vinik AI, Tsai ST, Moattari AR, Cheung P, Eckhauser FE, Cho K. Somatostatin analogue (SMS 201-995) in the management of gastroenteropancreatic tumors and diarrhea syndromes. Am J Med 1986;22:23-40.
7. Maton PN, O'Dorisio TM, Brent A, et al. Effect of a long-acting somatostatin analog (201-995) in a patient with pancreatic cholera. N Engl J Med 1985;312:17-21.
8. Santangelo WC, O'Dorisio TM, Kim JG, Severino G, Kreis GJ. Pancreatic cholera syndrome: Effect of a synthetic somatostatin analog on intestine water and ion transport. Ann Intern Med 1985;103:363-7.
9. Juby LD, Burke DA, Axon ATR. Somatostatin analogue SMS 201-995 long term therapy for vipoma. Postgrad Med J 1987;63:287-9.
10. Smith SS, Shulman DI, O'Dorisio TM, et al. Water diarrhea, hypokalemia, achlorhydria syndrome in an infant: Effect of the long-acting somatostatin analogue SMS 201-995 on the disease and linear growth. J Pediatr Gastroenterol Nutr 1987;6:710-6.
11. Edwards C, Cann PA, Read NW, Holdsworth CD. Effect of two new antisecretory drugs on fluid and electrolyte transport in a patient with secretory diarrhea. Gut 1986;27:581-5.
12. Cooper JC, Williams NS, King RFGJ, Barker MCJ. Effects of a long-acting somatostatin analogue in patients with severe ileostomy diarrhea. Br J Surg 1986;73:128-31.
13. Williams NS, Cooper JC, Axon ATR, King RFGJ, Barker M. Use of a long acting somatostatin analogue in controlling life threatening ileostomy diarrhea. Br Med J 1984;289:1027-8.
14. Lembeke B, Creutzfeldt W, Schleser S, Ebert R, Shaw C, Koop I. Effect of the somatostatin analogue sandostatin (SMS 201-995) on gastrointestinal, pancreatic and biliary function and hormone release in normal men. Digestion

1987;36:108-24.
15. Clements D, Elias E. Regression of metastatic vipoma with somatostatin analogue SMS 201-995. Lancet 1985;i:874-5.
16. Lamberts SWJ, Oosterom R, Neufeld M, Del Pozo E. The somatostatin analog SMS 201-995 induces long-acting inhibition of growth hormone secretion without rebound hypersecretion in acromegalic patients. J Clin Endocrinol Metab 1985;60:1161.
17. Lamberts SWJ, Uitterlinden P, Verschoor L, Van Dongen KJ, Del Pozo E. Long-term treatment of acromegaly with the somatostatin analogue SMS 201-995. N Engl J Med 1985;313:1576.
18. Ching LJC, Sandler LM, Kraenzlin ME, Burrin JM, Joplin GF, Bloom SR. Long term treatment of acromegaly with a long acting analogue of somatostatin. Br Med J 1985;290:284.
19. Tolis G, Yotis A, Del Pozo E, Pitoulis S. Therapeutic efficacy of a somatostatin analogue (SMS 201-995) in active acromegaly. J Neurosurg 1986;65:37.
20. Williams G, Ball JA, Burrin JM, Joplin GF, Bloom SR. Effective and lasting growth-hormone suppression in active acromegaly with oral administration of somatostatin analogue SMS 201-995. Lancet 1986;ii:774.
21. Barnard LB, Grantham WG, Lamberton P, O'Dorisio TM, Jackson IMD. Treatment of resistant acromegaly with a long-acting somatostatin analogue (SMS 201-995). Ann Intern Med 1986;105:856.
22. Sandler LM, Burrin JM, Williams G, Joplin GF, Carr DH, Bloom SR. Effective long-term treatment of acromegaly with a long-acting somatostatin analogue (SMS 201-995). Clin Endocrinol (Oxford) 1987;26:85.
23. Plewe G, Beyer J, Krause U, Neufeld M, Del Pozo E. Long-acting and selective suppression of growth hormone secretion by somatostatin analogue SMS 201-995 in acromegaly. Lancet 1984;ii:782.
24. Candrina R, Gussago A, Giustina G. Effect of a new long-acting somatostatin analogue (SMS 201-995) on glycemic and hormonal response to a mixed meal in acromegalic patients. J Endocrinol Invest 1988;11:21.
25. Köhler E, Duberow-Drewe M, Drewe J, et al. Absorption of an aqueous solution of a new synthetic somatostatin analogue administered to man by gavage. Eur J Clin Pharmacol 1987;33:167-71.

ABSTRACTS

Association between invasiveness, inflammation, desmoplasia and survival in colorectal cancer

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A multivariate analysis was used to test the prognostic importance of invasiveness, inflammatory reaction and amount of fibrous tissue at the tumour edge in 527 colorectal carcinomas. Allowance was made for clinicopathological stage, tumour site, histological type and grade. A poorly defined tumour border, lack of inflammatory reaction and pronounced desmoplasia at the tumour edge were all associated with unfavourable stage distribution and each of these features had an independent effect on prognosis.

J CLIN PATHOL 1989;42:162-6

Review of GI disorders related to diabetes mellitus

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Gastrointestinal disorders are extremely common in patients with diabetes mellitus; prevalence rates of 30 to 75% have been recorded. The most common disorders are gastroparesis, diarrhea and constipation. Symptoms range from mild to severe, with the most severely affected patients being at risk for protein calorie malnutrition. This paper presents an historical review of the major studies in this area as well as guidelines for nutritional assessment. Current methods for treatment of diabetic gastroparesis and related disorders are included with emphasis on nutritional support techniques. Practical outlines for glucose control in patients on total parenteral nutrition or enteral feeding and guidelines for transition from parenteral to oral diet are presented.

J PARENT ENT NUTR 1989;13:84-91

Vertical gastric plication for gastroesophageal reflux

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An operation has been devised to prevent gastroesophageal reflux in which a vertical partition is made parallel to the proximal gastric lesser curvature. This simple technique (in which the stomach is neither opened nor divided) prevents reflux by: increasing the effective length of the intra-abdominal esophagus; increasing the crural sling and mucosal flap valve effect; sharpening the angle of entry into the gastric reservoir; and creating a flutter valve and markedly reducing cross-sectional area along which reflux can occur. Animal experiments and results from 26 patients who underwent this operation are discussed.

ANN R COLL SURGEONS (ENGLAND) 1989;71:31-6